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ALS—dying forward, backward or outward?

Heiko Braak and colleagues (Amyotrophic lateral sclerosis—a model of corticofugal axonal spread. Nature Rev. Neurol. 9, 708–714; 2013)[1] present impressively detailed evidence in support of corticofugal spread – also known as the 'dying-forward' model of neurodegeneration, first proposed by Eisen and Weber[2] - in amyotrophic lateral sclerosis (ALS). Here, I propose a refinement that integrates both the 'dying-forward' and 'dying-back'[3] models: the corticofugal synaptopathy, or, 'dying-outward' hypothesis.

In any model of ALS, a number of fundamental features have to be reconciled: First, degenerative changes occur primarily in anterior horn cells and brainstem motoneurons that receive monosynaptic connections from motor cortex,[4] and in the corticospinal tract neurons within primary motor cortex. Second, in some variants of ALS, the disease only affects the corticospinal tract neurons[5], whereas in other variants, it only affects anterior horn cells, or affects corticospinal tract neurons only very late in the disease[6]. Third, ALS progresses contiguously between spinal, brainstem and cortical regions, in what has been termed a 'prion-like' pattern[7]. Fourth, cortical areas involved late in the disease are linked via long-range synaptic connections[1]. Last, humans are the only species affected by sporadic ALS and only nonhuman primate models of ALS have recapitulated features of the disease observed in humans[8].

An important component of the corticofugal model[1] is the axonal transport hypothesis, which identifies the importance of long-range axonal connections in disease propagation, but overlooks the synapse—the very reason for the existence of such connections. Not only does the developing synapse, or growth cone, function independently[9] but there is also evidence that synaptic autonomy continues into adulthood[10]. For example, synaptic prion-like proteins maintain activity-dependent changes in synaptic efficacy independently of nuclear transcription within neuronal somata. Furthermore, mitochondria, essential for calcium buffering and energy, are maintained autonomously within the presynaptic and postsynaptic compartments[11]. Such autonomy permits efficient long-distance neuronal communication, but there is a trade-off: the lysosomal housekeeping processes responsible for recycling biomolecules, organelles and cellular debris located within the distant soma function less efficiently. Consequently, abnormal conformational changes in prion-like proteins can replicate and propagate without control and dysfunctional mitochondria accumulate[10, 11]. The longer the axon and the larger the synapse, the more likely this autonomous process is to malfunction, hence the susceptibility of the monosynaptic cortico-motoneuronal synapse at the onset of ALS in man.

The cortico-motoneuronal synapse is a feature that distinguishes primates from other mammalian species, and the number of corticomotoneuronal synapses and length of axons in the corticospinal tract that distinguish humans from nonhuman primates[12]. Mutations in mitochondrial DNA have been implicated in motor neuron diseases[13] and ALS[14], and there is increasing evidence that the interaction between pathological synaptic mitochondria and synaptic prion proteins leads to neurodegeneration[11]. The cortico-motoneuronal synapse, therefore, is not only pivotal as the link between the corticospinal

tract and anterior horn cells but also; because of its vulnerability, it is an efficient *nidus* for neurodegeneration. Consequently, biomarkers that can detect changes in the integrity of the cortico-motoneuronal synapse[15] should be able to identify the very earliest stages of ALS, enabling early disease-modifying therapeutic interventions at a stage when they can make a significant impact on survival in this dreadful disease.

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